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REVIEW

Diabetes and liver disease: An ominous association

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Abstract Diabetes mellitus and advanced liver disease are associated with each other more frequently than expected by chance, and such an association carries a significant risk of morbidity and mortality. A metabolic pathway leading to advanced liver disease via fatty liver and steatohepatitis has been demonstrated, further supporting the possibility that cirrhosis may be a late complication of diabetes. In addition, an interaction between hepatitis C virus (HCV) and insulin resistance increases the overall prevalence of associated diseases, through largely unidentified mechanisms. Extensive prospective monitoring of non-alcoholic fatty liver disease cases, analysis of insulin signaling in HCV-infected patients using molecular biology techniques, and intervention studies, will help to clarify the mechanisms of action of the possible clinical strategies, the predictive value of biochemical, histological, and clinical markers, and the effectiveness of treatments available.

Introduction

The association between liver disease and diabetes mellitus (DM) is well known, the overall prevalence being significantly higher than that expected by a chance association of two very common diseases. The key role of the liver in blood glucose control—the hepatic metabolism of insulin—as well as the influence of liver disease on peripheral glucose metabolism and whole-body insulin sensitivity, contribute to DM in the presence of advanced liver disease. More recently, new insights into this association came from the recognition that: (a) DM itself may be a cause of liver disease, via non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cirrhosis, and ultimately hepatocellular carcinoma; (b) hepatitis C virus may have direct diabetogenic effects; and (c) post-transplantation DM is a major cause of morbidity and mortality in subjects following liver transplantation. We shall revise the most recent evidence for an association between DM and liver

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disease, with particular emphasis on the therapeutic aspects.

Diabetes in advanced liver disease

An insulin-resistant state may be demonstrated in approximately 80% of patients with cirrhosis, and 20—63% of them will develop DM (hepatogenous diabetes). The prevalence is largely dependent on the diagnostic criteria, etiology, and the time from the diagnosis of cirrhosis. Once cirrhosis is established, hyperglycemia develops in up to 20% of cases within 5 years, but the clinical characteristics and the course of diabetes are different from those observed in the absence of liver disease.

Patients acquiring diabetes as a result of cirrhosis differ from typical type 2 DM patients by having a lower prevalence of family history of diabetes and a lower risk of macro- and microangiopathic complications [1]. In a point-prevalence study, the prevalence of micro- and peripheral macroangiopathy and coronary heart disease in cirrhosis with DM was comparable to that of controls, and was significantly lower than that observed in randomly selected patients with type 2 DM [2]. In a retrospective/prospective study, the prognostic significance of DM was analyzed in a group of almost 400 patients with cirrhosis (25% with DM) [3]. The larger mortality rate in DM patients was not due to the classical diabetes-related complications, but to an increased risk of hepatocellular failure. The prognostic significance of DM was particularly relevant when patients who died of gastrointestinal bleeding were excluded. The long-term prognosis is thus determined to a greater extent by the primary hepatic disease and its complications, rather than by DM-related complications. The low prevalence of micro- and macrovascular disease may be related to a shorter duration of DM, which may be related in turn to a reduced life expectancy, as well as to liver disease-induced abnormalities (low cholesterol, low platelet count, etc.) protecting the cardiovascular system from atherosclerosis.

The ultimate stage of cirrhosis may be the development of hepatocellular carcinoma (HCC). DM is one of the most common complications observed in HCC, but very few data exist on the impact of DM on the survival of HCC patients. In HCC patients undergoing surgical or non-surgical therapy, DM is associated with a poorer long-term prognosis. This is not the result of DM enhancing the progression of HCC or its recurrence, but is due to the induction of a rapid decline in residual liver function; such an effect is influenced by treatment strategies and by tumor and/or cirrhosis-related factors [4,5].

Therapeutic implications

Any therapeutic intervention in patients with DM and cirrhosis must be evaluated in terms of risks and benefits. The relatively low impact of DM on prognosis is a reason for adopting a non-aggressive approach to metabolic control. It can rarely be achieved solely by diet, particularly as dietary restrictions should be avoided in hypercatabolic patients with cirrhosis. Oral hypoglycemic agents are contraindicated in the presence of advanced disease due to the possible risk of lactic acidosis (biguanides) or the potential toxic effects in the presence of reduced hepatic or renal metabolism (sulfonylureas) [6]. Thiazolidinediones are rarely used after the unfortunate experience with troglitazone [7]. Thus, insulin remains the elective treatment; however, insulin-resistance, a variable hepatic insulin metabolism, and difficulties in dietary management, make glucose control extremely difficult to achieve.

Acarbose may be a reasonable therapeutic option to improve postprandial glucose control in cirrhotic patients with insulin-treated DM [8]. In a recent study [9], acarbose was also tested for the treatment of cirrhotic patients with DM and low-grade hepatic encephalopathy in a placebo-controlled trial. Acarbose improved glucose control—mainly postprandial glucose—and reduced glycosylated hemoglobin without deleterious effects on liver function. This therapeutic option might thus be particularly appealing for improving hepatic encephalopathy.

Diabetes as a cause of liver disease

DM per se may generate liver disease of metabolic origin (the so-called NAFLD) (Table 1), in association with obesity, dyslipidemia and hypertension. NAFLD is now considered as the hepatic manifestation of the metabolic syndrome, and is present in approximately 80% of type 2 DM. The epidemiology, etiology and pathogenesis of NAFLD are beyond the scope of this review, and we invite the readers to refer to an excellent recent review article [10].

In NAFLD, DM constitutes a risk factor for NASH and advanced, progressive liver disease [11,12]. In 103 patients who underwent serial liver biopsies, diabetes ($P = 0.007$) and a low initial fibrosis stage